

### REMARKS

Applicant respectfully requests reconsideration. Claims 1 to 13, 15 to 21, 26, 28, 30, 34, 36, 38 to 41, and 44 to 48 were previously pending in this application. Claims 9, 11, 13, 17 to 21, 26, 28, 30, 34, 36, 38, 39, 41, and 44 to 48 are currently withdrawn. Claim 15 is canceled in this Amendment without prejudice or disclaimer. Applicant reserves the right to pursue the subject matter of the canceled claim in a related application.

Claims 1, 2, 5 to 7, and 9 to 13 have been amended. Claim 1 was amended to include the language “isolated anti-Tumor Necrosis Factor-alpha (anti-TNF-alpha) polypeptide” as proposed by the Examiner. Claim 1 also was amended to recite that at least one anti-TNF-alpha single domain antibody is a *Camelidae* variable domain derived from a heavy chain antibody devoid of a light chain (VHH) or a humanized *Camelidae* VHH. Claim 1 also was amended to recite that the polypeptide does not include a light chain. Support for those amendments is found throughout the originally-filed specification, for example, at page 14, lines 11 to 27, and at originally-filed claims 10 and 16.

Claims 2, 5, 6, 9, and 11 to 13 were amended by changing the language “corresponds [or corresponding] to a sequence represented by” to the language “comprises [or comprising] the amino acid sequence of.” The Examiner proposed that change. Claim 2 was also amended to include the language “at least one single domain antibody.”

In claim 7, the full term “anti-interferon-gamma” was added as proposed by the Examiner. Claim 12 was similarly amended.

Claim 10 was amended by changing the term “VHHs” to the term “VHH.” Claim 12 was amended by deleting the language “for simultaneous, separate or sequential administration to a subject.”

Claims 1 to 8, 10, 12, 16, 21, and 40 are pending and under consideration. No new matter has been added.

### Claim Objections

The Examiner objected to claim 1 because it lacked the full term for “TNF.” Action at page 3. Claim 1 has been amended to include the full term.

The Examiner objected to claim 2 because it recited the term “a” rather than the language “at least one.” Action at pages 3 to 4. Claim 2 has been amended to include the language “at least one.”

The Examiner objected to claim 5 because the term “correspond” was not grammatically correct. Action at page 4. That term has been deleted from claim 5.

The Examiner objected to claim 7 because it lacked the full term for “IFN.” Action at page 4. Claim 7 has been amended to include the full term. Claim 12 has also been amended to recite the full term for “IFN”.

The Examiner objected to claim 11 because it lacked the full term for “VHH.” Action at page 4. Claim 1 has been amended to include the full term.

Accordingly, applicant requests reconsideration and withdrawal of the claim objections.

### Double Patenting Rejections

The Examiner provisionally rejected claims 1 to 8, 10, 12, 15, 16, 21, and 40 as allegedly being unpatentable over claims 1 to 6, 8, 44, 47, and 66 of copending Application No. 10/534,349. Action at page 5. Applicant notes that the rejection is a provisional rejection. Applicant may file a terminal disclaimer when the claims are otherwise in allowable format (See MPEP § 804).

The Examiner provisionally rejected claims 1 to 8, 10, 12, 15, 16, 21, and 40 as allegedly being unpatentable over claims 1 to 15, 22, 25 to 39, and 46 of copending Application No. 11/788,832. Action at page 5. Applicant notes that the rejection is a provisional rejection. Applicant may file a terminal disclaimer when the claims are otherwise in allowable format (See MPEP § 804).

The Examiner provisionally rejected claims 1 to 8, 10, 12, 15, 16, 21, and 40 as allegedly being unpatentable over claims 10, 11, 22, 24, 25, 27, and 30 to 33 of copending Application No. 11/804,647. Action at page 6. Applicant notes that the rejection is a provisional rejection. Applicant may file a terminal disclaimer when the claims are otherwise in allowable format (See MPEP § 804).

#### Rejection under 35 U.S.C. § 101

The Examiner rejected claims 1, 2, 15, and 16 under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter. Action at page 7. The Examiner proposed adding the term “isolated” to distinguish the claimed polypeptides from naturally occurring products. Id. Solely to expedite prosecution, and not acquiescing to the rejection, claim 1 has been amended by adding the term “isolated” as proposed by the Examiner. Thus, this rejection is moot. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

#### Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claim 12 under 35 U.S.C. § 112, second paragraph, as allegedly “being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.” Action at page 8. Specifically, the Examiner objected to the claim language “for simultaneous, separate or sequential administration to a subject.” Id. The Examiner contended that “[i]t is unclear how a composition that comprises both an anti-TNF- $\alpha$  polypeptide and at least one single domain antibody as set forth [in claim 12] can be administered separately or sequentially.” Id.

Solely to expedite prosecution, and not acquiescing to the rejection, the language “for simultaneous, separate or sequential administration to a subject” has been deleted from claim 12. Thus, this rejection is moot. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1, 15, 21, and 40 under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 91/02078A1 to Rathjen et al. (“Rathjen”). Action at page 8. The Examiner alleged that Rathjen “teaches polypeptide ligands that bind to TNF-alpha and alter its biological activity, including single domain antibodies and polypeptides which are synthetic and analogous (i.e. homologous) to the ligands that bind to TNF . . . , thus meeting the limitations of claim 1 and 15.” Id. at page 9.

Solely to expedite prosecution, and not acquiescing the rejection, claim 1 has been amended to recite “[a]n isolated anti-Tumor Necrosis Factor-alpha (anti-TNF-alpha) polypeptide comprising at least one anti-TNF-alpha single domain antibody which is a *Camelidae* variable domain derived from a heavy chain antibody devoid of a light chain (VHH) or a humanized *Camelidae* VHH, wherein the polypeptide does not include a light chain.” Rathjen fails to show *Camelidae* VHHs or humanized *Camelidae* VHHs. Thus, Rathjen does not anticipate amended claim 1.

Claim 15 has been cancelled. Claims 21 and 40 both recite “anti-TNF-alpha polypeptide of claim 1.” Accordingly, Rathjen also does not anticipate claims 21 and 40. Applicant need not address the Examiner’s other allegations concerning other elements of claims 1, 21, and 40. Applicants do not acquiesce to those other allegations.

Applicant respectfully requests reconsideration and withdrawal of the anticipation rejection in view of Rathjen.

The Examiner rejected claims 1, 3, and 6 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,670,453 to Frenken et al. ("Frenken"). Action at page 10. The Examiner alleged that Frenken "teaches a multivalent antigen binding protein comprising a single polypeptide chain comprising, connected in series, two or more single domain binding units . . . and teaches a polypeptide corresponding to a sequence represented by SEQ ID NO: 35 . . ." Id. at pages 10 to 11.

Solely to expedite prosecution, and not acquiescing the rejection, claim 1 has been amended to recite "[a]n isolated anti-Tumor Necrosis Factor-alpha (anti-TNF-alpha) polypeptide comprising at least one anti-TNF-alpha single domain antibody which is a *Camelidae* variable domain derived from a heavy chain antibody devoid of a light chain (VHH) or a humanized *Camelidae* VHH, wherein the polypeptide does not include a light chain." Frenken fails to show *Camelidae* VHHs or humanized *Camelidae* VHHs. Thus, Frenken does not anticipate amended claim 1.

Claims 3 and 6 both depend from claim 1. Accordingly, Frenken also does not anticipate claims 3 and 6. Applicant need not address the Examiner's other allegations concerning other elements of claims 1, 3, and 6. Applicants do not acquiesce to those other allegations.

Applicant respectfully requests reconsideration and withdrawal of the anticipation rejection in view of Frenken.

#### Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 1, 3, 4, 7, 8, 12, and 40 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent 6,759,518 to Kontermann et al. ("Kontermann"). Action at page 12. The Examiner alleged that Kontermann "teaches polypeptide constructs comprising at least one or at least two single domain antibodies with at least two specificities...."

Id. at page 13. The Examiner further alleged that Kontermann “teaches that therapeutic targets for the single domain antibodies can be cytokines, such as TNF-alpha and IFN-gamma... and that another specificity can be serum albumin....” Id.

The Examiner noted that Kontermann “does not specifically teach a particular polypeptide construct with at least one single domain antibody directed against TNF-alpha and one directed against serum albumin or a particular construct with at least one single domain antibody directed against TNF-alpha and one directed against IFN-gamma.” Id.

Solely to expedite prosecution, and not acquiescing the rejection, claim 1 has been amended to recite “[a]n isolated anti-Tumor Necrosis Factor-alpha (anti-TNF-alpha) polypeptide comprising at least one anti-TNF-alpha single domain antibody which is a *Camelidae* variable domain derived from a heavy chain antibody devoid of a light chain (VHH) or a humanized *Camelidae* VHH, wherein the polypeptide does not include a light chain.”

Kontermann fails to show, and would have failed to suggest, *Camelidae* VHHs or humanized *Camelidae* VHHs. Thus, Kontermann would not have rendered claim 1 obvious.

Claims 3, 4, 7, 8, and 12 depend from claim 1. Also, claim 40 recites “anti-TNF-alpha polypeptide of claim 1.” Accordingly, Kontermann would not have rendered obvious any of those claims. Applicant need not address the Examiner’s other allegations concerning other elements of claims 1, 3, 4, 7, 8, 12, and 40. Applicants do not acquiesce to those other allegations.

Applicant respectfully requests reconsideration and withdrawal of the obvious rejection over Kontermann.

The Examiner rejected claim 2 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kontermann in view of U.S. Patent No. 7,368,111 to Thompson et al. (“Thompson”). Action at page 14. The Examiner noted that Kontermann did not teach the particularly claimed

sequences in claim 2. Id. In view of the Examiner's construction of claim 2, the Examiner alleged that Thompson teaches the claimed sequences. Id. at pages 14 to 15.

First, Thompson would have failed to remedy the deficiencies of Kontermann with respect to claim 1 as discussed above. Accordingly, because claim 2 depends from claim 1, the combination of Kontermann and Thompson would have failed to render obvious claim 2. Second, claim 2 has been amended as suggested by the Examiner to further clarify the claimed sequences.

Applicant need not address the Examiner's other allegations concerning other elements of claim 2. Applicants do not acquiesce to those other allegations.

Applicant respectfully requests reconsideration and withdrawal of the obviousness rejection over Kontermann and Thompson.

The Examiner rejected claim 5 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kontermann in view of U.S. Patent No. 7,084,257 to Deshpande et al. ("Deshpande"). Action at page 15. The Examiner noted that Kontermann did not teach the particularly claimed sequences in claim 5. Id. at page 16. In view of the Examiner's construction of claim 5, the Examiner alleged that Deshpande teaches the claimed sequences. Id.

First, Deshpande would have failed to remedy the deficiencies of Kontermann with respect to claim 1 as discussed above. Accordingly, because claim 5 depends from claim 1, the combination of Kontermann and Deshpande would have failed to render obvious claim 5. Second, claim 5 has been amended as suggested by the Examiner to further clarify the claimed sequences.

Applicant need not address the Examiner's other allegations concerning other elements of claim 5. Applicants do not acquiesce to those other allegations.

Applicants request reconsideration and withdrawal of the obviousness rejection over Kontermann and Deshpande.

The Examiner rejected claims 10 and 16 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kontermann in view of EP 584421 to Casterman et al. ("Casterman"). Action at page 17.

The Examiner noted that Kontermann did not "teach that the single domain antibodies can be Camelidae heavy chain antibodies." Id. The Examiner, however, alleged that "upon reading the disclosure of the Kontermann et al. patent, the skilled artisan would have recognized the desirability of developing protein constructs that are less immunogenic for human use." Id. The Examiner then alleged that Casterman "teaches that heavy chain single domain antibodies from camelids are desirable and teaches that these antibodies can be humanized, and thus would be less immunogenic for human use . . . ." Id.

The Examiner then alleged that

"it would have been reasonable to predict that humanized camelidae heavy chain antibodies could be successfully incorporated into the constructs of Kontermann et al. Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to improve Kontermann et al.'s single domain antibody constructs as disclosed by Casterman et al. to yield predictable results."

Id. at pages 17 to 18. Finally, the Examiner alleged that "[s]uch would amount to a simple substitution of known equivalents to obtain predictable results." Id. at page 18.

Solely to expedite prosecution, and not acquiescing the rejection, claim 1 has been amended to recite "[a]n isolated anti-Tumor Necrosis Factor-alpha (anti-TNF-alpha) polypeptide comprising at least one anti-TNF-alpha single domain antibody which is a *Camelidae* variable domain derived from a heavy chain antibody devoid of a light chain (VHH) or a humanized *Camelidae* VHH, wherein the polypeptide does not include a light chain."



Kontermann describes single-chain antigen-binding molecules that require a heavy chain and a light chain. “The present invention relates to a single-chain multiple antigen-binding molecule with diverse variable domains of a heavy and of a light chain of an immunoglobulin, which are connected in the form of a VH-VL construct, which are in turn connected together via a peptide.” Kontermann at column 4, lines 35 to 39.

In contrast, claim 1 of the present application recites that the anti-TNF-alpha polypeptide does not include a light chain. Casterman would not have taught one of ordinary skill in the art to delete the light chains in the Kontermann single-chain antigen-binding molecules. Accordingly, the combination of Kontermann and Casterman would have failed to render obvious claim 1.

Claims 10 and 16 depend from claim 1. Accordingly, Kontermann and Casterman would not have rendered obvious those claims. Applicant need not address the Examiner's other allegations concerning other elements of claims 10 and 16. Applicants do not acquiesce to those other allegations.

Applicant respectfully requests reconsideration and withdrawal of the obvious rejection over Kontermann and Casterman.

**CONCLUSION**

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. A0848.70005US00.

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Respectfully submitted,

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